

Prognosis Value of Plasma S100B Protein Levels after Subarachnoid Aneurysmal Hemorrhage

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Background: S100B has been described as a biologic marker of neuronal damage. The purpose of this study was to assess its prognostic value in patients with subarachnoid aneurysmal hemorrhage.

Methods: Seventy-four patients (32 men and 42 women; age, 48 ± 11 yr) admitted within 48 h after subarachnoid hemorrhage onset and treated by surgical clipping or coiling within 2 days after admission were included. World Federation of Neurological Surgeons, Fisher, and Glasgow outcome scores at intensive care unit discharge and at 6 months were evaluated. Blood concentrations of S100B were determined at admission and daily up to day 8.

Results: The time course of S100B was increased in patients with high World Federation of Neurological Surgeons and Fisher scores. Patients who underwent surgical clipping had an S100B time course longer than that of those who underwent coiling. This difference remained true after stratification for World Federation of Neurological Surgeons and Fisher scores. The threshold of mean daily value of S100B predicting a poor outcome at 6 months was 0.4 µg/l (sensitivity = 0.50 [95% confidence interval (CI), 0.29-0.71], specificity = 0.67 [95% CI, 0.76-0.95]). In multivariate analysis, high World Federation of Neurological Surgeons score (odds ratio = 9.5 [95% CI, 3.1-29.4]), mean daily S100B value above 0.4 µg/l (odds ratio = 7.3 [95% CI, 2.3-23.6]), and age (odds ratio = 1.08 per year [95% CI, 1.01-1.15]) were independent predictors of a poor 6-month outcome (Glasgow outcome score 1-3).

Conclusion: Mean daily value of S100B assessed during the first 8 days is a prognostic tool complementary to initial clinical evaluation in subarachnoid hemorrhage patients.

S100 PROTEINS are a group of calcium-binding proteins present in cell cytosol.^{1,2} They are dimeric, consisting of two subunits, α and β. S100B (αβ or ββ) is present in high concentrations in astroglial and Schwann cells of the central and peripheral nervous systems. S100B pro-

tein serum concentration has been extensively studied in severe head trauma,³⁻⁹ acute ischemic stroke^{8,10} and cardiac arrest.³ Regarding subarachnoid aneurysmal hemorrhage (SAH), S100B has been evaluated in blood,^{9,11} cerebrospinal fluid,^{9,12-15} and microdialysis perfusate.¹⁶ From studies performed in SAH and including large series of patients, it can be stated that S100B correlates with neurologic deficit at admission and outcome. Some indirect data argue for an increase in S100B when vasospasm occurs.¹⁷ In all studies but the one by Wiesmann *et al.*,¹¹ cerebrospinal fluid rather than serum concentration was measured. However, to be clinically relevant and to reduce the risk of infection due to manipulation of cerebrospinal fluid shunt, preferably S100B should be measured in blood. In the study by Wiesmann *et al.*, samplings were performed at admission, day 3, and day 7, and this could be regarded as long intervals between samplings given the short half-life of the molecule. Moreover, little information regarding treatment was given, although it can be hypothesized that most of these patients underwent conventional surgery at the time of inclusion. Treatment strategy (surgery *vs.* coiling), therapeutics in the intensive care unit, and management of major complications such as cerebral vasospasm have changed to a great extent in the past decade.¹⁸ For all of these reasons, we thought it necessary to reappraise the usefulness of daily S100B dosages in SAH and to further study its relation with clinical and computed tomography (CT) evaluations as well as with treatment strategy and outcome. We made the hypothesis that an increased S100B value during the first 8 days might be an independent predictor of a poor outcome.

Materials and Methods

The study was approved by our local ethical committee (Comité de Protection des Personnes, Pitié-Salpêtrière, Paris, France). In accordance with the Helsinki Declaration, written informed consent was obtained from the patient or patient's next of kin.

Patients

The inclusion period was from December 2003 through October 2004. Inclusion criteria were clinical history of SAH within the last 2 days before admission with evidence of bleeding on CT and presence of an aneurysm at cerebral angiography, age 18 yr or older, and treatment by surgery or coiling within the 48 h after

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admission. All patients were admitted to our neurosurgical intensive care unit after initial treatment. Exclusion criteria were admission later than 48 h after bleeding, surgery or coiling later than 48 h after admission, and therapeutic abstention decision.

Clinical and CT Evaluation

At admission, clinical severity was assessed using the World Federation of Neurological Surgeons (WFNS) score¹⁹ as follows: 1 = Glasgow coma scale (GCS) score of 15, no motor deficit; 2 = GCS score of 13-14, no motor deficit; 3 = GCS score of 13-14 and any motor deficit or aphasia; 4 = GCS score of 7-12, with or without motor deficit; and 5 = GCS score of 3-6, with or without motor deficit. Hemodynamic status was evaluated by clinical examination, arterial blood gas analysis, chest radiograph, and echocardiograph when appropriate. Cardiac troponin Ic blood concentration (Stratus Analyzer; Dade, Massy, France) was systematically measured. The initial CT was reviewed by an independent radiologist blinded to clinical history, therapeutics, and S100B values and classified according to the modified Fisher score as follows: grade 1 = no subarachnoid blood; grade 2 = broad diffusion of subarachnoid blood; grade 3 = with clots or thick layers of blood; grade 4 = intraventricular hemorrhage or intracerebral hematoma, no clot; and grade 5 = intraventricular hemorrhage or intracerebral hematoma with clot.²⁰ Neurologic outcome was assessed using the Glasgow outcome scale (GOS) score²¹ at discharge from the intensive care unit and at 6 months by a same anesthesiologist (CC). GOS was defined as follows: 1 = death; 2 = persistent vegetative state; 3 = severe disability; 4 = moderate disability; and 5 = good recovery.

Clinical Management

The type of treatment (surgery or coiling) was decided according to both location and size of the aneurysm by the neurosurgeon and the neuroradiologist. Coiling was preferred for patients in whom it was deemed feasible.²² Surgery was performed in the remaining cases. All patients received intravenous nimodipine at a dose of 2 mg/h from admission until at least completion of the study, except during periods of uncontrolled increased intracranial pressure during which intravenous nimodipine was discontinued. Seizures were systematically prevented by gabapentin (600 mg \times 3, per os). A central venous and an arterial catheter were inserted in most of the patients before and/or after surgery or coiling. Normovolemia was maintained through the systematic administration of intravenous physiologic electrolyte solution at 1,000-2,000 ml/day and colloids if necessary. Additional fluids were given in case of hypovolemia diagnosed on clinical symptoms and increased systolic pressure variation. After treatment, systolic arterial blood pressure was maintained above 130-160 mmHg by con-

tinuous infusion of norepinephrine as needed. Great caution was taken to avoid hyperthermia (above 38.5°C) and hyperglycemia (above 7.5 mm) through the administration of acetaminophen and insulin as needed. In ventilated patients, arterial carbon dioxide partial pressure (Paco₂) was maintained between 35 and 40 mmHg, and peripheral oxygen saturation (SpO₂) was maintained above 97%. Oral or enteral nutrition was begun as soon as possible. An external ventricular drain (Sophysa, Orsay, France) was inserted in case of hydrocephaly on CT and in patients with a high WFNS grade (WFNS score of 3-5). The line was connected to an external pressure strain gauge to continuously monitor intracranial pressure according to a recently published protocol.²³ Increased intracranial pressure was treated by cerebrospinal fluid drainage, mechanical ventilation, reinforcement of sedation, and, rarely, moderate hypothermia. CT was performed whenever clinical deterioration occurred to search for secondary complications such as hydrocephalus or ischemia.

Vasospasm was suspected on clinical deterioration, fever, appearance of new symptoms (cephalgia, confusion, seizure, or motor deficit), mean transcranial Doppler velocities above 120 cm/s or a daily change in mean transcranial Doppler velocities above 50 cm/s,²⁴ and confirmed by cerebral angiography. Each vasospasm episode was treated with intraarterial administration of nimodipine as recently described.²⁵ This therapy was repeated if necessary. Angioplasty was used as a second-line therapy when nimodipine was judged insufficient.

S100B Protein Measurement

A venous blood sample for S100B level determination was systematically withdrawn each day from day 1 to day 8. The first sample was taken within 12 h after admission. By reference, the first 24 h after admission defined day 1. Venous blood was collected on blood collection devices and centrifuged within 2 h (1,800 g for 10 min at +4°C). S100B concentrations were measured with an immunoluminometric sandwich assay on a LIA-mat 300 analyzer (Byk-Sangtec France Laboratories, Le Mée sur Seine, France) using the manufacturer's reagents.²⁶ Briefly, tubes coated with anti-S100B chain were incubated with 100 μ l per tube of samples for 60 min. After the tubes were washed, aminobutylethylisoluminol-labeled anti-S100B was added for 120 min and, after a final washing step, the luminescence of aminobutylethylisoluminol when oxidized in the presence of deuterioferriheme and hydrogen peroxide was measured. The amount of S100B in the samples was calculated using standard curves prepared with calibrators with known concentrations of the proteins. The detection limit of the assay is 0.02 μ g/l. Values in healthy individuals are considered to be below 0.15 μ g/l. Intra-assay and interassay coefficient of variation of the measurement were less than 7 and 9%, respectively.

Statistical Analysis

In patients who did not complete the 8-day period because their good clinical status allowed them to be discharged from the intensive care unit to the ward or because death occurred within the study period, the last value obtained was taken to replace missing values until day 8 in the statistical analysis according to the neighboring nonmissing values method.

For statistical purposes, WFNS, Fisher, and GOS scores were dichotomized (WFNS score of 1-2 *vs.* WFNS score of 3-5, Fisher score of 1-3 *vs.* Fisher score of 4-5, and GOS score of 4-5 *vs.* GOS score of 1-3). Initial S100B values were compared between groups by analysis of variance and the Fisher exact method. The effects of WFNS score, Fisher score, GOS score, treatment, and spasm on S100B concentrations over time were analyzed by two-way repeated-measures analysis of variance for one grouping factor, *i.e.*, WFNS (WFNS score of 1-2 *vs.* WFNS score of 3-5) and for one within factor, *i.e.*, time (day 1 to day 8).

The receiver operating characteristic (ROC) curves were used to determine the best threshold for initial and mean daily values of S100B to predict poor outcome. Assessment of the diagnostic performance of initial and mean daily values of S100B was analyzed by calculating the sensitivity, specificity, positive and negative predictive values, accuracy, and their 95% confidence intervals (CIs). For clinical reasons, specificity was preferred to sensitivity to determine the best threshold, *i.e.*, we choose the threshold that maximally reduced the number of patients having a good outcome despite a mean daily value of S100B above threshold.

After dichotomization of the mean daily values of S100B in two groups (according to the results of the previous analysis), contingency tables were used for the following categorical variables: initial WFNS and Fisher scores, age (below and above 50 yr), aneurysm location (middle cerebral artery *vs.* others), troponin Ic levels (below and above 0.10 $\mu\text{g/l}$), vasospasm (present or absent at angiography), and type of treatment (coiling *vs.* surgery).

A first multivariate analysis was performed using backward stepwise logistic regression where all of the variables suggested by the univariate analysis ($P < 0.2$) were entered into the model to predict an increased mean daily value of S100B. A second multivariate analysis including dichotomized mean daily S100B as a variable was performed to predict outcome at 6 months. Calibration and discrimination of the logistic models were assessed using Hosmer-Lemeshow statistics and ROC curves, respectively.

Data are expressed as mean \pm SD. All tests were two sided, and a P value of less than 0.05 was considered significant. Statistical analyses were performed using JMP IN 5.1 statistical software (SAS Institute Inc., Cary, NC).

Table 1. Baseline Clinical Characteristics (n = 74)

Variable	Number of Patients (%)	
WFNS initial score		
1	25 (33)	
2	19 (26)	
3	6 (8)	
4	11 (15)	
5	13 (18)	
Fisher initial score		
1	5 (7)	
2	11 (15)	
3	18 (24)	
4	24 (32)	
5	16 (22)	
	At Discharge	At 6 Months
GOS score		
1	14 (20)	15 (20)
2	—	—
3	17 (23)	9 (12)
4	13 (17)	11 (15)
5	30 (40)	39 (53)
Treatment		
Coiling	53 (72)	
Surgery	21 (28)	
	Coiling	Surgery
Location and treatment*		
ICA + PCA	23 (43)	2 (10)
Ca + Ant Co	21 (40)	3 (14)
MCA	6 (11)	16 (76)
Basilar troncus	2 (4)	—
Vertebral artery	1 (2)	—

World Federation of Neurological Surgeons (WFNS) and Fisher scores were measured at admission.

* $P < 0.001$ between coiling and surgery.

Ant Co = anterior communicating artery; Ca = cerebral anterior artery; ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior communicating artery.

Results

During the study period, 101 patients were admitted to our intensive care unit with an SAH diagnosis. Of these, 27 were excluded for the following reasons: delay of more than 48 h between admission and onset of symptoms ($n = 16$), delay of more than 48 h between admission and date of intervention ($n = 7$), or no surgical or endovascular treatment ($n = 4$). Eventually, 74 patients were included (mean age, 48 ± 11 yr; 32 men and 42 women). Among these, 53 patients (72%) underwent coiling and 21 patients (28%) underwent surgical clipping. Table 1 shows the main characteristics of this population. Patients with middle cerebral artery aneurysms underwent surgery more often than coiling, whereas the opposite was true for all of the other locations.

Of these 74 patients, 14 stayed less than 8 days in the intensive care unit because of death ($n = 5$) or early discharge to ward ($n = 9$). Among these, 4 patients had values until day 7, 5 until day 6, 3 until day 5, and 2 until day 4. Values of S100B continued to increase in patients

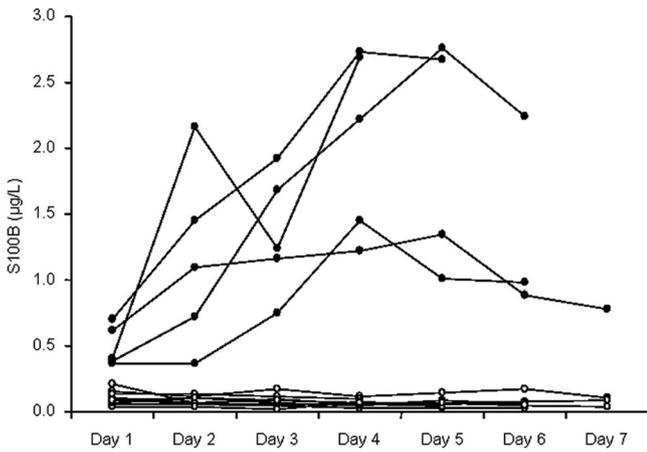


Fig. 1. S100B individual data for the 14 patients who stayed less than 8 days in the intensive care unit because of an early discharge to the ward (n = 9, empty circles) or death (n = 5, filled circles).

who finally died contrary to those who were discharged from the intensive care unit before day 8 who maintained low values over time (below 0.4 µg/l; $P < 0.001$; fig. 1). Figure 2 shows S100B values according to WFNS score, Fisher score, and location of the aneurysm. For the initial S100B value, there were significant differences between groups for both WFNS and Fisher scores but not for location of the aneurysm. The time course of S100B was significantly different between patients with low and high WFNS and Fisher scores ($P < 0.01$). Significant differences were observed in the time course of

S100B between the three locations of the aneurysm ($P < 0.02$), the highest values being observed in patients with a middle cerebral artery aneurysm, intermediate values being observed in patients with aneurysms of the anterior circulation, and the lowest values being observed in patients with internal carotid or posterior communicating artery aneurysms.

The initial troponin Ic value was significantly linked to the S100B initial value stratified into three groups (initial value < 0.2 µg/l, between 0.2 and 0.4 µg/l, and > 0.4 µg/l; fig. 3A). There were significant differences in S100B time course between patients with low and high initial troponin Ic values ($P = 0.03$; fig. 3B).

S100B time course values were significantly higher in patients who underwent surgical clipping than in those who underwent coiling, and this difference remained true after stratification for WFNS and Fisher scores (figs. 4A and B). As shown in table 2, the percentage of patients having a mean daily value of S100B above the threshold of 0.4 µg/l was higher in patients with high WFNS and Fisher scores, with a middle cerebral artery aneurysm, with a high troponin Ic value at admission, and treated surgically. In the multivariate analysis, only surgery (odds ratio = 6.1; 95% CI, 1.7-21.9) remained independently associated with a mean daily value of S100B above the threshold of 0.4 µg/l.

As shown in figure 5A, S100B initial values were significantly correlated with outcomes at discharge and at 6 months (both $P < 0.03$). As shown in figure 5B, S100B

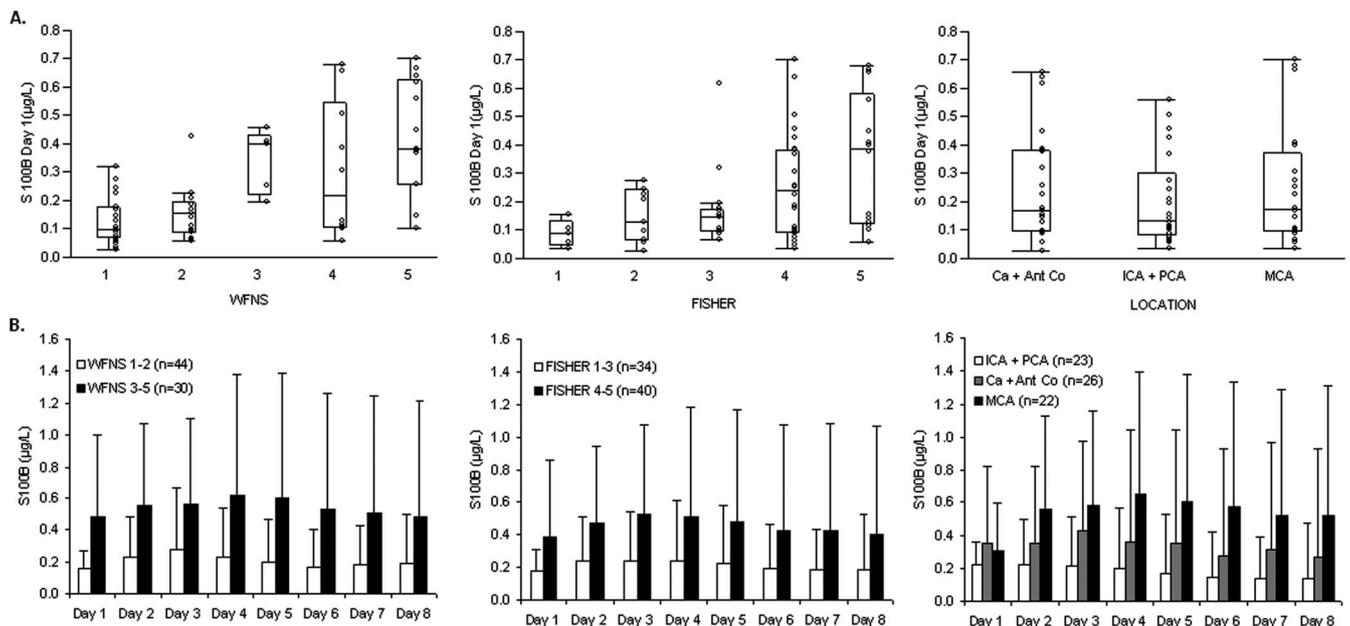


Fig. 2. (A) Correlations between initial S100B value (µg/l) and World Federation of Neurological Surgeons (WFNS) and Fisher scores ($P < 0.01$) as well as location of the aneurysm (not significant). For graphical reasons, three patients were excluded from the representation. Statistical analysis was performed with the totality of the patients. (B) S100B time course values (µg/l) according to WFNS and Fisher scores as well as location of the aneurysm. The box plots summarize the distribution of points at each factor level. The ends of the box are the 25th and 75th quartiles. The line across the middle of the box identifies the median sample value. The whiskers extend from the ends of the box to the outermost data point that falls within the distances computed. Repeated measures were all significant ($P < 0.02$). Ant Co = anterior communicating artery; Ca = cerebral anterior artery; ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior communicating artery.

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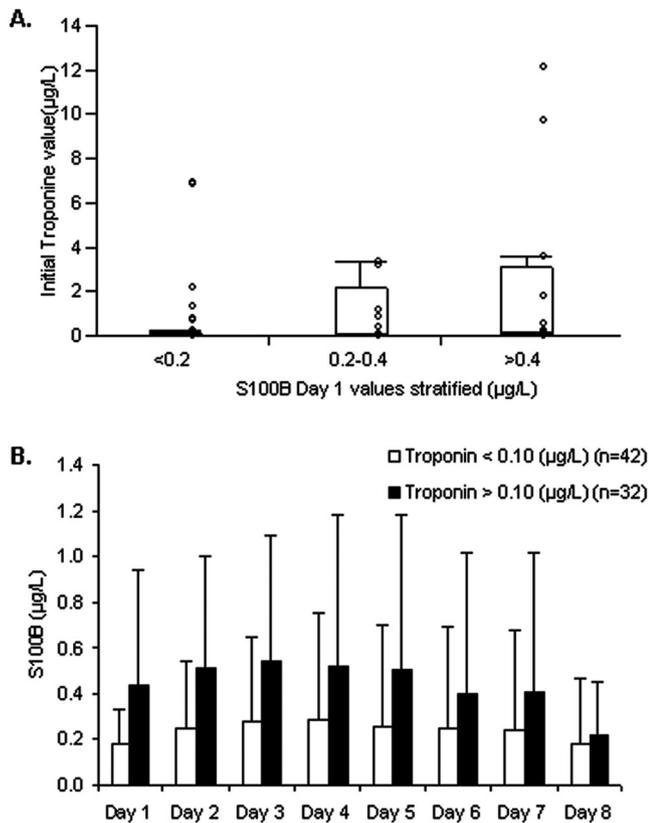


Fig. 3. Initial troponin Ic values *versus* initial S100B value ($\mu\text{g/L}$) ($P < 0.01$; A) and *versus* S100B time course ($P < 0.03$; B). The box plots summarize the distribution of points at each factor level. The ends of the box are the 25th and 75th quartiles. The line across the middle of the box identifies the median sample value. The whiskers extend from the ends of the box to the outermost data point that falls within the distances computed.

time course was also significantly correlated with outcome scores at discharge from the intensive care unit and at 6 months. WFNS score, Fisher score, mean daily S100B values above $0.4 \mu\text{g/L}$ (all $P < 0.001$), initial S100B values above $0.4 \mu\text{g/L}$ ($P < 0.01$), age ($P < 0.05$), and initial troponin value ($P < 0.05$) were significantly correlated with outcome at 6 months in the univariate model. Neither the location nor the type of treatment and the occurrence of spasm were predictive factors. As shown in table 3, after multivariate analysis, the initial WFNS score, a mean daily S100B value above $0.4 \mu\text{g/L}$, and age were significantly predictive of outcome at 6 months. Calibration and discrimination of the model were appropriate as shown by the Hosmer-Lemeshow statistic (4.17; $P = 0.84$) and the area under the ROC curve (0.88; 95% CI, 0.80–0.96).

The ROC curve showed that initial and mean daily values of S100B significantly predicted a poor outcome (fig. 6). The area under the curve was significantly higher for the mean daily value of S100B. The diagnostic performances of initial and mean daily values of S100B above $0.4 \mu\text{g/L}$ in predicting a poor outcome are shown in table 4. This threshold of $0.4 \mu\text{g/L}$ was chosen to provide a high specificity. In contrast, the threshold of

$0.2 \mu\text{g/L}$ was the one that minimized the distance to the ideal point (sensitivity = specificity = 1) on the ROC curve. For this threshold of $0.2 \mu\text{g/L}$, specificity and sensitivity were both of 0.62 for the initial value and of 0.72 and 0.79 for the mean daily value, respectively. A threshold of $0.5 \mu\text{g/L}$ for the mean daily value increased specificity to 0.92 but reduced sensitivity to 0.29.

Finally, the S100B time course was not significantly different in patients with ($n = 27$, 36%) and without vasospasm ($n = 47$, 64%), although this was not true when this analysis was performed in the subgroup of patients having an initial S100B value below $0.4 \mu\text{g/L}$ (data not shown). Among patients with a diagnosed vasospasm, 17 patients maintained daily S100B below $0.4 \mu\text{g/L}$ over time, and none of these patients died. Ten patients had at least one value of S100B above this threshold, and five of them died.

Discussion

Our data confirm that S100B serum concentrations correlate well with initial SAH severity evaluated either clinically (WFNS grading scale) or by CT (Fisher score). Furthermore, the mean value computed during the first 8 days was an independent predictive factor for GOS outcome at 6 months.

To our knowledge, except for three studies in which SAH patients were analyzed together with various neurologic disorders,^{27–29} only four studies^{11–14} and a recent case report¹⁶ have specifically addressed the usefulness of S100B level measurement in patients with SAH. These studies had variable S100B sampling (with sometimes a lack of precision regarding timing and number of samples) as well as heterogeneous clinical evaluation and treatment procedures. For all of these reasons, comparison with the current set of data is difficult. The only study with an important series of SAH patients using plasma rather than cerebrospinal fluid S100B or extracellular fluid (microdialysis) measurements was performed by Wiesmann *et al.*¹¹ Our study confirms their observation correlating initial S100B values and clinical condition. In addition, our results show that the time course of S100B measured over an 8-day period correlates with WFNS and Fisher scores indicating a long-lasting effect of the initial neurologic injury induced by bleeding. Together, patients with middle cerebral artery aneurysm had higher S100B concentrations over time as compared with other locations. This is concordant with our current knowledge regarding the influence of aneurysm location on outcome.^{30,31} Indeed, in the retrospective study from Kopera *et al.*,³¹ 32% of the patients with a middle cerebral aneurysm had intracranial hemorrhage, a known predictive factor for poor outcome.³² S100B time course correlated better with WFNS and Fisher scores as well as location than the initial value *per se*.

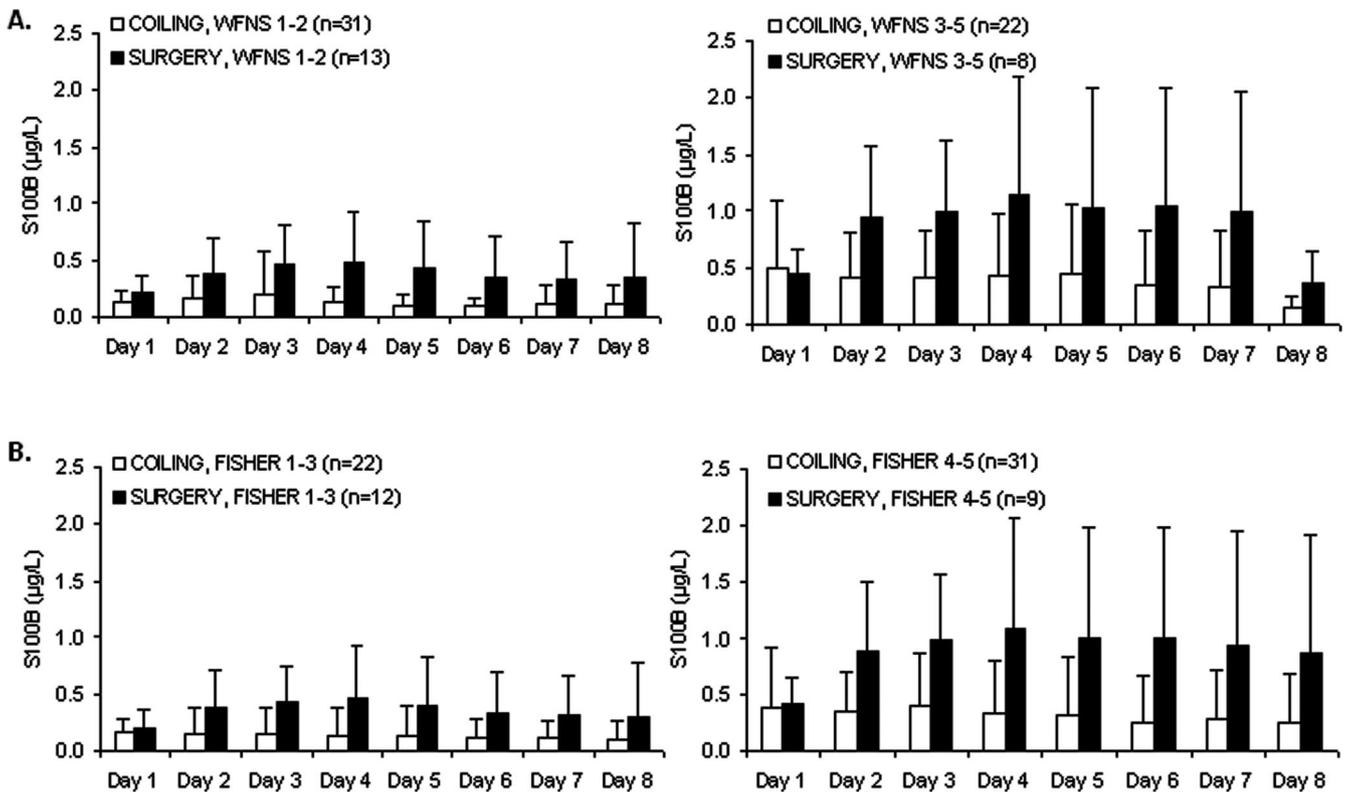


Fig. 4. S100B serum concentration time course after coiling ($n = 53$) or neurosurgery ($n = 21$) according to the initial World Federation of Neurological Surgeons (WFNS) (A) or Fisher (B) scores. Left and right figures in each panel represent S100B time course for good initial clinical scores (WFNS 1–2 or Fisher 1–3) and poor initial clinical scores (WFNS 3–5 or Fisher 4–5). All differences each day were significant ($P < 0.05$).

S100B time course was significantly correlated with initial troponin Ic values: Patients with high initial troponin Ic ($> 0.10 \mu\text{g/l}$) had also higher levels of S100B over time. This result is in accordance with previous studies where high troponin levels have been linked with the occurrence of neurologic deficit.^{33,34} This also confirms the fact that SAH is a multiorgan dysfunction entity whose consequences may involve other organ systems, such as the cardiovascular system.³⁵

Table 2. Comparison of Patients with and without Increased S100B Mean Daily Values

Variable	Mean Daily S100B $< 0.4 \mu\text{g/l}$ ($n = 56$)	Mean Daily S100B $\geq 0.4 \mu\text{g/l}$ ($n = 18$)	P Value
WFNS score 1 or 2	38 (67)	6 (33)	0.002
Fisher score 1–3	30 (53)	4 (22)	0.01
Age < 50 yr	30 (53)	10 (55)	NS
Location, MCA vs. others	12 (21)	10 (55)	0.05
Initial troponin Ic $< 0.10 \mu\text{g/l}$	37 (66)	5 (27)	0.004
Type of treatment, coiling	45 (80)	8 (44)	0.01
Spasm	36 (64)	11 (68)	NS

Data are number of patients (%).

MCA = middle cerebral artery; NS = not significant; WFNS = World Federation of Neurological Surgeons.

Major differences were found in S100B time course between patients treated by coiling compared with those who underwent surgery. Indeed, although departing at equivalent values, S100B plasma concentration decreased significantly more rapidly in coiled patients compared with those who underwent clipping. This was all the more true after stratification according to the initial WFNS or Fisher grading. If these results were to be confirmed, they would argue for a neuroprotective effect of coiling in SAH. These data are concordant with the results of the International Study of Aneurysm Treatment trial²² that demonstrated that coiling improved by 23% the chances for an independent survival at 1 yr as compared with clipping in patients with ruptured aneurysms, mostly in good clinical grades. Nevertheless, it should be pointed out that the decision to perform coiling whenever possible may have introduced a selection bias in our study. Regarding the multivariate analysis that considered all factors potentially correlated with S100B mean daily values, only the type of treatment (surgery vs. coiling) was significant. This suggests that coiling reduces brain damage as compared with surgical clipping. Some authors have suggested that surgery by itself may increase S100B through the nonspecific secretion of an astrocyte.³⁶ However, this explanation seems incompatible with the duration of

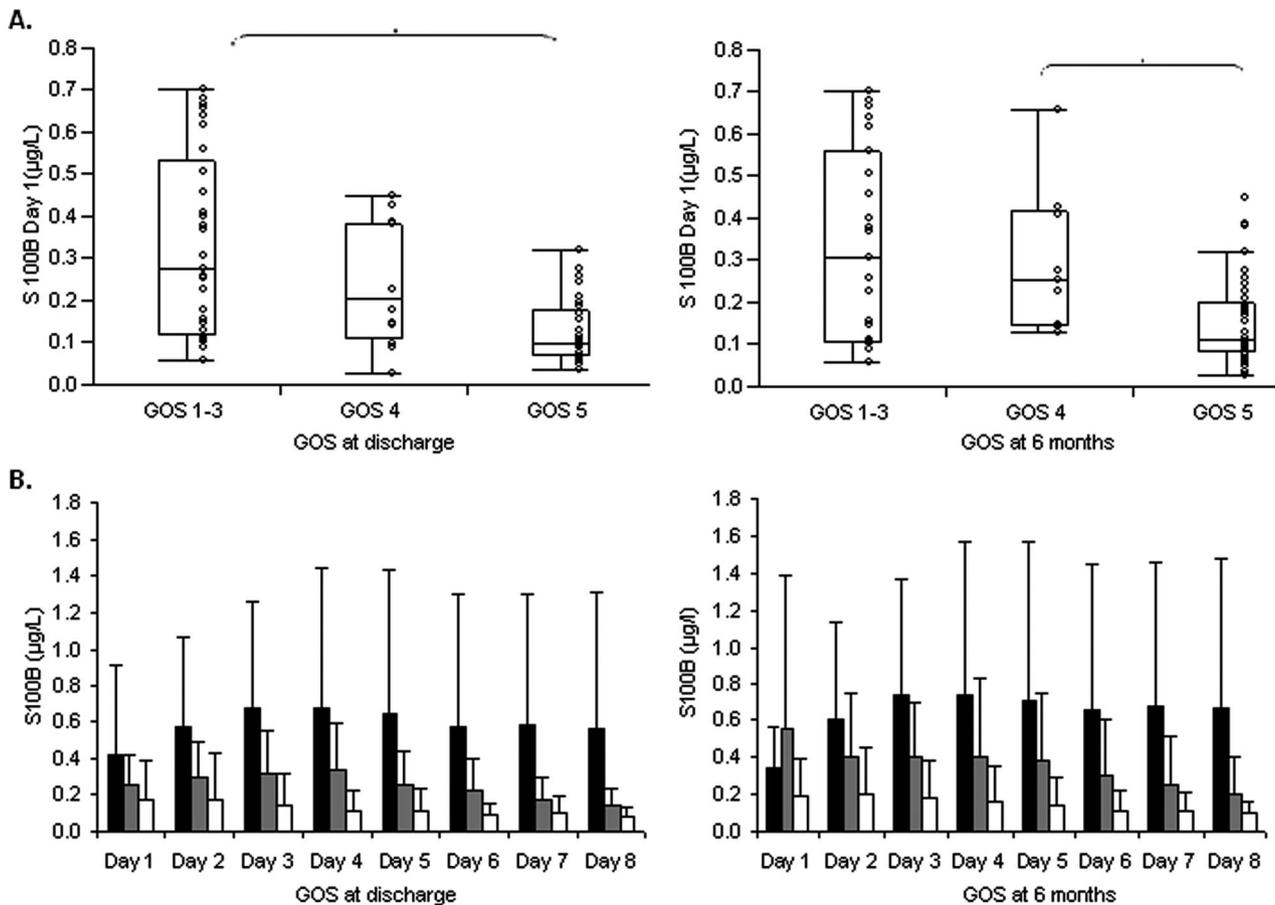


Fig. 5. (A) S100B day 1 value according to the outcome at intensive care unit discharge (*left*) and at 6 months (*right*). * $P < 0.03$. For graphical reasons, two patients were excluded from the figures. The *box plots* summarize the distribution of points at each factor level. The *ends of the box* are the 25th and 75th quartiles. The *line* across the middle of the box identifies the median sample value. The *whiskers* extend from the ends of the box to the outermost data point that falls within the distances computed. Statistical analysis was performed with the totality of the patients. (B) S100B time course values according to outcome at discharge (*left*) and at 6 months (*right*). *Black bars* represent Glasgow outcome scale (GOS) scores of 1–3, *gray bars* represent GOS scores of 4, and the *white bars* represent GOS scores of 5 (both repeated measures $P < 0.001$).

increased S100B values after surgery, lasting the entire study period.

Our results show that a time course evaluation of S100B has a useful and independent prognostic value to assess outcome in SAH patients. Indeed, initial and mean daily values above $0.4 \mu\text{g/l}$ significantly predicted a poor outcome. This threshold is close to the one defined by Raabe *et al.*³⁶ at $0.5 \mu\text{g/l}$ for various neurologic disorders and by Foerch *et al.*³⁷ at $0.35 \mu\text{g/l}$ in ischemic stroke. Decreasing the cutoff to $0.2 \mu\text{g/l}$ improved the sensitivity at the price of the specificity. Moreover, age, WFNS initial score, and mean daily S100B value above $0.4 \mu\text{g/l}$

Table 3. Multivariate Analysis of Risk Factors for Poor Outcome at 6 Months (n = 74)

Variable	Odds Ratio (95% Confidence Interval)	P Value
WFNS score (by 1 point increase)	2.5 (1.5–4.1)	0.001
Mean daily S100B > $0.4 \mu\text{g/l}$	4.4 (1.1–17.5)	0.037
Age (per year)	1.08 (1.01–1.15)	0.027

WFNS = World Federation of Neurological Surgeons.

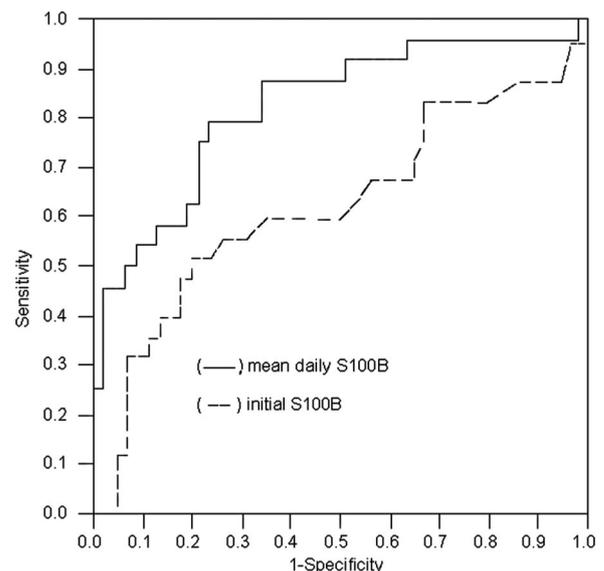


Fig. 6. Receiver operating characteristic curves of initial value (*dotted line*) and mean daily value (*continuous line*) of S100B during the 8 first days after admission and outcome at 6 months (Glasgow outcome scale score of 1–3 vs. Glasgow outcome scale score of 4–5).

Table 4. Comparison of Diagnostic Performance of Initial versus Mean Daily Value of S100B (n = 74)

	S100B Initial Value	S100B Mean Daily Value
Sensitivity	0.41 (0.22–0.63)	0.50 (0.29–0.71)
Specificity	0.86 (0.73–0.94)	0.87 (0.76–0.95)
Positive predictive value	0.59 (0.32–0.81)	0.63 (0.38–0.83)
Negative predictive value	0.75 (0.62–0.85)	0.78 (0.65–0.88)
Accuracy	0.72 (0.60–0.80)	0.74 (0.63–0.82)
Area under the curve	0.67 (0.55–0.77)	0.80 (0.69–0.88)*

Data are values (95% confidence interval). The cutoff value for S100B was 0.4 µg/l.

* $P < 0.05$ vs. initial value.

were the three independent predictors of outcome at 6 months. This is in accordance with a recent published case report suggesting S100B protein as a surrogate marker of brain injury.¹⁶

In our study, direct relation between S100B values and vasospasm episodes remain unclear. However, the power of our study may have been insufficient to detect a significant association. Moreover, it should be pointed out that the initial surge of S100B could “mask” in some manner the evidence of secondary ischemic complications as assessed by a secondary increase in S100B.

Regarding the limitations of our study, a more prolonged study period might have likely increase the prognostic value of S100B time course because some patients might have experienced late-onset vasospastic episodes that could also impair the prognosis. It must also be stated that because of the very short half-life of S100B, estimated at 2 h,³⁸ we cannot exclude that transient surges in S100B were missed with the once-daily measure that we used in our study.

In conclusion, measurement of S100B plasma concentration is a good indicator of severity and an independent predictor of 6-month outcome in SAH patients. Multiple daily measurements with rapid results are already available, thus giving the opportunity for clinicians to strictly monitor brain ischemia in SAH patients. Similar to troponin and heart disease,³⁹ S100B may be an important biologic marker for the future improvement of clinical management and outcome in SAH patients.

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